Remarks/Arguments

Claims 119-123 are pending in this application. Claim 119 has been amended.

I. 35 U.S.C. §§ 101 and 112, First Paragraph –Utility/Enablement

Claims 119-123 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicants strongly disagree and, therefore, respectfully traverse the rejection.

Applicants submit that the data presented in Example 170 starting on page 539 of the specification, and the cumulative evidence of record, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention. Applicants rely upon the gene amplification data of the PRO1153 gene for patentable utility of the claimed PRO1153 polypeptides. This data is clearly disclosed in the instant specification in Example 170, which discloses that the gene encoding PRO1153 showed significant amplification in primary lung tumors. As disclosed in previous response on record, Applicants submit that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly over expressed and has utility in the diagnosis of lung cancer or for individuals at risk for developing lung cancer.

As further support for their utility claim, Applicants have submitted a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. According to the Goddard Declaration, the 2.0-fold to 2.9-fold amplification of PRO1153 in adenocarcinomas or squamous cell carcinomas of the lung would be considered significant and credible by one skilled in the art, based upon the facts disclosed therein. The

Examiner has not provided any evidence to show that the disclosed DNA amplification is not significant.

The Examiner asserts that basis of the rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels. (Page 3 of the instant Office Action).

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (submitted with Response of June 16, 2004) collectively teach that in general, gene amplification increases mRNA expression.

Further, Applicants have submitted Declarations of Dr. Paul Polakis (made of record Response of June 16, 2004 and Preliminary Amendment of June 30, 2006), which teach that, in general, there is a correlation between mRNA levels and polypeptide levels. Applicants would also like to bring to the Examiner's attention a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9). Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO1153 polypeptide to refute Appellant's assertion of a correlation between DNA levels, mRNA levels and protein expression.

Applicants further submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede to), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Applicants submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna et al. (made of record in the Response submitted June 16, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation

between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as exemplified by the teachings of Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, the art in general overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung cancers.

Accordingly, Applicants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed antibodies to PRO1153 polypeptides.

The Examiner has further asserted that "[o]nly two out of the fourteen lung cancer samples tested positive. Therefore, if a sample were taken from an individual with actual lung cancer, ***it is more likely than not that this assay would yield a false negative result****" (Page 4 of the instant Office Action, emphasis in original).*

Applicants emphasize that they have shown significant DNA amplification in two of the lung tumor samples in Table 9, Example 170 of the instant specification. The fact that not all lung tumors tested positive in this study does not make the gene amplification data less significant. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. For example, the article by Hanna and Mornin (of record), discloses that the known breast cancer marker HER-2/neu is "amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma" (page 1, col. 1). In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are useful for better classification of tumors. Therefore, whether the PRO1153 gene is amplified in two lung tumors or in all lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO1153 is considered significant is what lends support to its usefulness as a tumor marker.

The Examiner has also asserted that "[t]he data presented in the specification were not corrected for aneuploidy" and cites a references by Hittelman et al. and Sen et al. in support of the assertion that "[a] slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid." (Pages 5 and 6 of the instant Office Action).

Applicants submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Applicants' Response filed June 16, 2004),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

The Examiner has asserted that "[s]ignificant further research is would have been required of the skilled artisan to reasonable confirm that PRO1153 is overexpressed in any cancer to the extent that I could be used as a cancer diagnostic agent, thus the asserted utility is not substantial." (Page 8 of the instant Office Action).

As discussed in previous responses of record, M.P.E.P. §2107.01 cautions Office personnel not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an Appellant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[1] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[2] gives the following instruction to patent examiners: "If the

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[1] M.P.E.P. §2107.01.

Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Applicants' position is based on the overwhelming evidence from gene amplification data disclosed in the specification which clearly indicate that the gene encoding PRO1153 is significantly amplified in certain lung tumors. Based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO1153 gene is amplified, the PRO1153 polypeptide would be more likely than not over-expressed. Thus, data relating to PRO1153 polypeptide expression may be used for the same diagnostic and prognostic purposes as data relating to PRO1153 gene expression. Therefore, based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed antibodies to the PRO1153 polypeptide, because the current invention is fully enabled by the disclosure of the present application.

Accordingly, Applicants submit that based on the general knowledge in the art at the time the invention was made and the teachings in the specification, the specification provides clear guidance as to how to interpret and use the data relating to PRO1153 polypeptide expression and that the claimed antibodies to the PRO1153 polypeptide have utility in the diagnosis of cancer.

A *prima facie* case of lack of utility has not been established

Applicants respectfully submit that the Examiner has not made a proper *prima facie* showing of lack of utility, because the Examiner has not shown that Applicants' asserted utility is more likely than not incorrect.

The Examiner asserts that "[t]he art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels", citing Pennica, Konopka, Sen, Godbout and Li (pages 5-8 of the instant Office Action).

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA

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[2] M.P.E.P. §2107 II(B)(1).

and polypeptide levels. As discussed in the previous responses of record, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants have previously cited Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* as collectively teaching that in general, gene amplification increases mRNA expression. Applicants' arguments presented in the previously filed Response submitted June 16, 2004 and Preliminary Amendment submitted July 11, 2007are hereby incorporated by reference in their entirety.

Pennica *et al.*

The Examiner has cited the abstract of Pennica *et al.* for its disclosure that "WISP-2 genomic DNA was amplified in colon cancer cell lines and in human colon tumors, but RNA expression was reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." (Page 5 of the instant Office Action). From this, the Examiner has concluded that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist.

Nowhere in the Pennica paper does the author suggest that it is more likely than not that altered mRNA levels does not correlate with altered protein levels. On the contrary, there is a statement in Pennica that says "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression...*" (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added), which implies

that the mRNA/protein correlation does exist, even if not always, but "always" is not required by the utility standard.

The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . ." (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added). Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

Konopka *et al.*

The Examiner has also citeded the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to gene amplification but to variation in the level of mRNA produced from a single genomic template." (Page 6 of the instant Office Action).

Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka *et al.* does not disclose any generalized teaching about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results with the *abl* gene alone. Nor does Konopka *et al.* support the PTO's position that DNA amplification is not correlated with mRNA overexpression. Konopka *et al.* show only that, of the cell lines known to have increased abl protein expression, only one had amplification of the abl gene (page 4051, col. 1). This result proves only that increased mRNA and protein expression levels can result from causes other than gene amplification. Konopka *et al.* do not demonstrate that when gene amplification does occur, it does not result in increased mRNA and protein expression levels, particularly given that the cell line with amplification of the abl gene did show increased abl mRNA and protein expression

levels. Applicants further submit that, contrary to the PTO's assertions, Konopka *et al.* supports Applicants' position that mRNA levels correlate with protein levels. Konopka *et al.* states that "the 8-kb mRNA that encodes $P210^{c\text{-}abl}$ was detected at a 10-fold higher level in SK-CML7bt-333 (Fig. 3A, +) than in SK-CML16Bt-1 (B, +), which **correlated** with the relative level of $P210^{c\text{-}abl}$ detected in each cell line. Analysis of additional cell lines demonstrated that the level of 8-kb mRNA **directly correlated** with the level of $P210^{c\text{-}abl}$ (Table 1)" (page 4050, col. 2, emphasis added).

Thus, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to single genes or genes within a single family and thus, their teachings have been misinterpreted in this rejection.

Godbout *et al.*

Regarding Godbout, the Examiner has asserted that Godbout et al. teaches that "a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The Examiner further asserts that Godbout teaches "[i]t is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell." (Page 6 of the instant Office Action).

Applicants have previously made of record three more recent references, published in 2002, by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al*, (made of record in Applicants' Response filed on June 16, 2004), which collectively teach that in general, gene amplification increases mRNA expression. Applicants submit that these more recent references must be acknowledged as more accurately reflecting the state of the art regarding the correlation between gene amplification and transcript expression than the references cited by Godbout *et al.* Nevertheless, Applicants maintain that Godbout *et al.* report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Moreover, selective advantage to cell survival is not the only mechanism by which genes impact cancer. Mechanistic data is not a requirement for the utility requirement. Hence, this rejection is improper. Applicants respectfully submit that, as discussed above, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (of record), collectively teach that gene amplification increases mRNA expression for large numbers of genes, which have not been identified as being

oncogenes or as conferring any selective growth advantage on tumor cells. Thus, the art of record clearly shows that there is no requirement that a polypeptide must be a known oncogene or a protein otherwise known to be associated with tumor growth, in order for amplification of the gene encoding the protein to correlate with increased protein expression. In fact, as demonstrated by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, examination of gene amplification is a useful way to identify novel proteins not previously known to be associated with cancer.

Li *et al.*

The Examiner also cites Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 7 of the instant Office Action). Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). In fact, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Applicants' previous responses, and in the Goddard Declaration of record, an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above, the PRO1153 gene showed 2.0 fold to 2.9-fold amplification in adenocarcinomas or squamous cell carcinomas of the lung, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not disprove that a gene with a substantially higher level of gene amplification, such as PRO1153, would be expected to show a corresponding increase in transcript expression.

The Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the cited articles do not provide sufficient reasons to doubt the statements by Applicants that PRO1153 has utility. As discussed above, the law does not require that DNA amplification

is "always" associated with overexpression of the gene product. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

It is "more likely than not" for amplified genes to have incrased mRNA and protein levels

As discussed above and in detail previously, Applicants have provided ample evidence in the form of articles from the art, like Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and over a 100 references and Declarations by experts in the field of oncology and gene expression, i.e.: the Declarations by Dr. Audrey Goddard, Dr. Paul Polakis (I and II) and Dr. Avi Ashkenazi, to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the encoded protein will also be expressed at an elevated level.

The Examiner contends that the Polakis Declaration is insufficient to overcome the rejection of claims 119-123 since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels. The examiner further alleges that the declaration lacks factual support for the expert's opinion. In the same paragraph, the Examiner acknowledges that the Goddard declaration speaks to the utility and enablement of amplified genes, yet it is alleged that Goddard does not speak to whether or not the encoded proteins are also found at increased levels in cancerous tissues. (Pages 9-10 of the instant Office Action).

Applicants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels. To address the Examiner's concern as to "whether or not a 2.01 to 2.52-fold amplification of the gene encoding PRO1153 in two lung tumors is significant" (page 9 of the instant Office Action), Applicants previously submitted the Goddard declaration which was presented to support the basis for using relative gene copy number, as quantitated by the TaqMan PCR technique, as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Further, the correlation between gene amplification and mRNA levels has already been established by the data shown in the Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* articles. It is not necessary for any one

Declaration or reference to address each and every issue in the rejection. Such a requirement is unreasonable because neither the law nor the Utility Guidelines requires it.

Applicants further emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells.

Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[3] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[4] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[5]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[6] which

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[3] *In re Rinehart,* 531 F.2d 1084, 189 U.S.P.Q. 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 U.S.P.Q. 881 (Fed. Cir. 1985).

[4] *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)).

[5] *In re Alton, supra.*

[6] Part IIB, 66 Fed. Reg. 1098 (2001).

state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

The statement in question from an expert in the field (the Polakis Declaration) states that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell."

Therefore, barring evidence to the contrary regarding the above statement in the Polakis Declaration, this rejection is improper under both the case law and the Utility guidelines. As discussed above, the arguments presented by the Examiner in combination with the cited articles do not provide sufficient reasons to doubt the statements by Applicants that PRO1153 has utility.

With respect to the evidence provided by Orntoft et al. Hyman et al. and Pollack et al., the Examiner asserts that "Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO1153 in the instant specification. That is, it is not clear whether or not PRO1153 is in a gene cluster in a region of a chromosome that is highly amplified." (Page 11 of the instant Office Action).

Applicants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed in Applicants' previous Responses Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

Applicants note that Orntoft *et al.* also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis, and that this analysis was done on a gene by gene basis, with the authors selecting 40 well resolved abundant known proteins for which to assess the correlation between mRNA and protein levels for each gene. The authors found that "[i]n general **there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations**. Only one gene [of the 40 examined] showed disagreement between transcript alteration and protein alteration" (page 42, col. 2; emphasis added). Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

The Examiner next asserts that "Orntoft et al. could only compare the levels of about 40 well-resolved and focused abundant proteins." (Page 13 of the instant Office Action; emphasis in original).

As discussed above, Orntoft *et al.* found that the level of gene amplification associated with expression changes was only around two-fold, even less than the 2.014-fold to 2.87-fold amplification observed for PRO1153. Even with these relatively low levels of gene amplification, Orntoft *et al.* found that "**[i]n most cases,** chromosomal gains detected by CGH were accompanied by an increased level of transcripts in both TCCs 733 (77%) and 827 (80%)" (page 40, col. 2; emphasis added). The level of correlation between DNA copy number and increased mRNA levels observed by Orntoft *et al.*, from **77-80%**, clearly meets the standard of more likely than not. Orntoft *et al.* also found a "highly significant" correlation between mRNA and protein levels, with the two data sets studied having correlations of 39/40 (**98%**) and 19/26 (**73%**) (pages 42-43).

With respect to Hyman et al., the Examiner asserts that the Hyman reference teaches that "[l]ess than half (44%) of highly amplified genes showed mRNA overexpression (abstract)." (Page 12 of the instant Office Action).

Applicants submit that the Examiner's assertion is not consistent with the interpretation Hyman *et al.* themselves place on their data, stating that, "The results illustrate **a considerable influence of copy number on gene expression patterns**." (Page 6242. col. 1; Emphasis added). In the more detailed discussion of their results, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (***i.e.*, belonged to the global upper 7% of expression ratios**) compared with only 6% for genes with normal copy number." (See page 6242, col. 1; Emphasis added). These details make it clear that Hyman *et al.* set a highly restrictive standard for considering a gene to be overexpressed; yet almost half of all highly amplified transcripts met even this highly restrictive standard. Therefore, the analysis performed by Hyman *et al.* clearly shows that it is "more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner has alleged that "Pollack et al also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not

investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention." (Page 12 of the instant Office Action).

Applicants maintain that Pollack *et al.* profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression. As stated above, the Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* articles were submitted to support the correlation between gene amplification and mRNA levels, which according to the Examiner is the sole basis of the maintained rejections.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the claimed PRO1153 polypeptides have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the claimed antibodies to the PRO1153 polypeptide for diagnosis of cancer.

II. 35 U.S.C. §101 – Product of Nature

Claim 119 stands rejected under 35 U.S.C. §101 for allegedly containing non-statuatory subject matter. (Page 15 of the instant Office Action).

As per the Examiner's suggestion, Applicants have amended the claims to indicate the hand of the inventor by inserting the term "isolated" into claim 19 when referring to the antibody.

Applicants therefore respectfully request the Examiner to withdraw the rejection of Claims 119-123 under 35 U.S.C. §101.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **07-1700** Attorney Docket No.: **123851-181895 (formerly 39780-2730P1C32)**.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: March 26, 2008

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